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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/203,004	02/28/94	BERD D	1225/0C674

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EXAMINER	
UNGAR, S	
ART UNIT	**PAPER NUMBER**
1642	41

DATE MAILED: 03/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/203,004	Applicant(s) Berd
	Examiner Ungar	Group Art Unit 1642

☒ Responsive to communication(s) filed on *Jan 14, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *43, 44, 47, and 49-77* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *43, 44, 47, and 49-77* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Amendment filed November 4, 1999 (Paper No. 38) in response to the Office Action of April 28, 1999 (Paper No. 36) is acknowledged and has been entered. The Amendment (Paper No. 39) and the Terminal Disclaimer (Paper No. 40) filed January 14, 2000, in response to the telephone interview of January 13, 2000 (Paper No. 38.5) have been entered Previously pending claims 63 and 73 have been canceled, claims 44, 47, 64, 74 and 76 have been amended and new claim 77 has been added. Claims 43, 44, 47 49-62, 64-72 and 74-77 are currently being examined.

2. The Terminal Disclaimer filed January 14, 2000 is acceptable.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following rejections are being maintained:

Claim Rejections - 35 USC § 103

5. Claims 47 and 65-76 remain rejected for the reasons previously set forth in Paper No. 36, Sections 10 , pages 8-12.

Applicant argues that (a) the legal test for obviousness cannot be established by combining teachings of the prior art absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so, (b) Murphy and or Berd fail to teach a method of treatment for non-melanoma malignant tumors in a human patient, (c) the antibody patents which merely teach conventional methods for generating antibodies provide no missing teaching, (d) Geczy fails to provide any teaching pertinent to the claimed compositions and methods.

The arguments have been considered but have not been found persuasive because (a') contrary to the assertion of Applicant, the test for obviousness is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art, (b') Applicant is arguing limitations not recited in the claims as currently constituted. The claims are drawn to a method of treating a malignant tumor in a human patient and as broadly written, read on the treatment of melanoma (b'-d') Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981), (c') multiple immunizations are conventional in the art for producing all forms of immune response, (d') Geczy clearly teach the equivalence of CDNB and FDNB. The references teach not only the suggestion but also the means and motivation to successfully treat melanoma by sensitizing with FDNB and administering cyclophosphamide prior to administering DNP-conjugated tumor cells and an adjuvant, which treatment results in the claimed T-cell dependent responses. Applicant's arguments have not been found persuasive and the rejection is maintained.

6. Claims 47 and 65-76 remain rejected for the reasons previously set forth in Paper No. 36, Sections 11 , pages 12-15.

Applicant argues that, for the reasons set forth above, the rejection is in error. The argument has been considered but has not been found persuasive for the reasons set forth above. Applicant's arguments have not been found persuasive and the rejection is maintained.

7. Claims 43, 44, 47 and 49-76 remain rejected for the reasons previously set forth in Paper No. 36, Sections 12 , pages 15-18.

Applicant argues that (a) there is no reasonable expectation of successfully implementing the vaccination program described with respect to melanoma in Berd to other tumor types because this reference provides "preliminary" results that "may represent a significant advance in the immunotherapy of human melanoma and thus it lacks any reasonable expectation of an effective treatment for tumors in general or even melanoma in particular, (b)Wiseman does not supply the missing teaching and teaches an alternative form of immunotherapy that depends on the route of administration, (c) even if combined, the lack of any reasonable expectation of success from the disclosure of Berd precludes determining that the invention is obvious.

The arguments have been considered but have not been found persuasive because (a) Berd et al clearly teach that treatment of melanoma patients with autologous vaccine preceded by low dose CY induces DTH to melanoma cells and regression of metastatic tumors. The reference is specifically drawn to increasing the efficiency of the process by sensitizing with DNCB and immunizing with tumor

cells conjugated to DNP. Clearly, one would have an expectation of success since it was already known that immunization with tumor cells alone, after pretreatment with CY resulted in regression of metastatic tumors. Further, it was clearly demonstrated that a patient developed erthema, followed by ulceration and drainage of necrotic material in > 50 large dermal metastasis and that at the time of publication, some of the metastasis were beginning to regress, Further the reference specifically teaches that tumors were infiltrated with activated T lymphocytes, that the tumor masses developed a striking inflammatory response and that the patients developed DTH, (b') regardless of the route of administration, Wiseman clearly teaches that treatment of patients with lung, colon and kidney cancer with autologous tumor cell vaccine preceded by low dose CY leads to prolonged survival. It would have been expected that vaccines using other types of tumor cells, shown to effectively treat cancer, would behave in a mechanistically similar manner to the melanoma vaccine described in Berd et al where it was shown that administration of the DNP-conjugated reagent led to DHT against melanoma cells, infiltration of the tumors by activated T lymphocytes, inflammation in the tumor masses, especially in view of the fact that there is no teaching of any no distinguishing features of melanoma tumor cells which would lead one to expect that there would be a difference in the immune response to this type of tumor cell in particular, (c') Berd et al clearly demonstrate the successful use of the composition and the method. Applicant's arguments have not been found persuasive and the rejection is maintained.

8. Claims 43, 44, 47 and 49-76 remain rejected for the reasons previously set forth in Paper No. 36, Sections 13 , pages 18- 21.

Applicant argues that Berd, 1983 is cumulative to the teaching of Berd, 1989 and that Berd 1983 does not supply any of the other missing teachings that are not supplied by the combination of Berd, the antibody Patents and Geczy and that in particular, the reference does not provide any teaching concerning a haptenized tumor cell vaccine or methods of treating cancer using such a vaccine. The argument has been considered but has not been found persuasive for the reasons drawn to the lack of persuasiveness of Applicant's arguments drawn to Berd, the antibody Patents and Geczy disclosed above and further because, Berd, 1983 is cited because it is drawn to treatment of breast cancer patients with autologous vaccine. The substitution of the breast cancer cells of Berd 1983 for the melanoma cells of Berd, 1989 in the method and composition of Berd 1989 was *prima facie* obvious for the reasons set forth in Paper No. 36. Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). Applicant's arguments have not been found persuasive and the rejection is maintained.

9. Claims 43, 44, 47 and 49-76 remain rejected for the reasons previously set forth in Paper No. 36, Sections 14 , pages 21-25.

Applicant argues that (a) the deficiencies of Berd, the antibody Patents and Geczy have been addressed above, (b) Sanda and Moody fail to supply the missing teachings and propose an alternative cancer therapy and neither references provides any motivation to decorate the tumor cells with hapten in order to elicit an effective immune response. The arguments have been considered but have not been found persuasive because (a') for the reasons set forth above, (b') the combined references make the invention obvious for the reasons set forth previously and in particular Berd supplies the motivation to "decorate the tumor cells with hapten" in order to elicit an effective immune response, see above.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. Claims 43, 49-51, 54-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising the claimed tumor cell conjugate and an adjuvant, does not reasonably provide enablement for a composition comprising the claimed tumor cell conjugate alone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to treatment of malignant tumors with a composition comprising a hapten conjugated to a tumor cell. The specification teaches a melanoma vaccine administered with BCG and describes immune responses to the

melanoma vaccine administered with BCG (page 19-43) and specifically teaches in the sentence bridging pages 27-28 that "all vaccines were DNP-conjugated and mixed with BCG". It appears that the inclusion of an adjuvant may be a critical step since Livingstone et al (of record) disclosed that in a melanoma vaccine using the GM2 ganglioside, antibody responses were not induced unless BCG was added to the purified GM2 vaccine (p. 2913, paragraph bridging columns 1 and 2). Livingstone et al also state that "adjuvants ..... were important factors in the mouse studies and results of the present human trials indicate their importance in melanoma patients". Further, Hoover et al, of record, also used BCG as an adjuvant in a colorectal cancer vaccine and states that the correct amount of the appropriate adjuvant was a critical condition of the success of the immunotherapy (p. 1242, col 1, para 2). Based on the teachings above and in the specification one of skill in the art would not expect that the claimed composition could be used as contemplated for the treatment of malignant tumors without specifically including an adjuvant as demonstrated in the specification. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

11. Claims 70 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of cyclophosphamide administration "only" prior to the first administration of said composition has no clear support in the specification and the claims as originally filed. The specification teaches that cyclophosphamide is administered 3 days prior to each vaccine administration (p. 44, lines 26-27) but does not specifically state that the cyclophosphamide is only administered prior to vaccine. The subject matter

claimed in claims 47-58 broadens the scope of the invention as originally disclosed in the specification.

12. Claims 57, 66 and 70 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 57 is indefinite because there is no antecedent basis for the term "cancer" in claim 44 from which claim 57 depends.

Claim 66 is indefinite because there is no antecedent basis for the term "cancer" in claim 47 from which claim 66 depends.

Claim 70 is indefinite because there is no antecedent basis for the phrase "wherein said therapeutically effective amount of cyclophophamide" in claim 47 from which claim 70 depends. Further, the claim is indefinite as the term "cyclophophamide" appears to be a misspelling of the term cyclophosphamide.

Claim Rejections - 35 USC § 103

13. Claim 77 is rejected under 35 USC 103 for the reasons previously set forth in Paper No. 36, Sections 10 , pages 8-12 and above drawn to the rejection of claims 47 and 65-76.

The claim is drawn to the method of claim 47 wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.

The claim is obvious for the reasons previously set forth. Applicant's arguments are relevant to the instant rejection. The arguments drawn to the rejection of claims 47 and 65-76 under 35 USC 103 are relevant to the instant

rejection. The arguments have been considered but have not been found persuasive for the reasons set forth above.

14. Claim 77 is rejected under 35 USC 103 for the reasons previously set forth in Paper No. 36, Sections 11 , pages 12-15 and above drawn to the rejection of claims 47 and 65-76.

The claim is drawn to the method of claim 47 wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.

The claim is obvious for the reasons previously set forth. Applicant's arguments are relevant to the instant rejection. The arguments drawn to the rejection of claims 47 and 65-76 under 35 USC 103 are relevant to the instant rejection. The arguments have been considered but have not been found persuasive for the reasons set forth above.

15. Claim 77 is rejected under 35 USC 103 for the reasons previously set forth in Paper No. 36, Sections 12 , pages 15-18 and above drawn to the rejection of claims 43, 44, 47 and 49-76.

The claim is drawn to the method of claim 47 wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.

The claim is obvious for the reasons previously set forth. Applicant's arguments are relevant to the instant rejection. The arguments drawn to the rejection of claims 43, 44, 47 and 49-76 under 35 USC 103 are relevant to the

instant rejection. The arguments have been considered but have not been found persuasive for the reasons set forth above.

16. Claim 77 is rejected under 35 USC 103 for the reasons previously set forth in Paper No. 36, Sections 13 , pages 18-21 and above drawn to the rejection of claims 43, 44, 47 and 49-76.

The claim is drawn to the method of claim 47 wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.

The claim is obvious for the reasons previously set forth. Applicant's arguments are relevant to the instant rejection. The arguments drawn to the rejection of claims 43, 44, 47 and 49-76 under 35 USC 103 are relevant to the instant rejection. The arguments have been considered but have not been found persuasive for the reasons set forth above.

17. Claim 77 is rejected under 35 USC 103 for the reasons previously set forth in Paper No. 36, Sections 14 , pages 21-25 and above drawn to the rejection of claims 43, 44, 47 and 49-76.

The claim is drawn to the method of claim 47 wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8+CD4-.

The claim is obvious for the reasons previously set forth. Applicant's arguments are relevant to the instant rejection. The arguments drawn to the rejection of claims 43, 44, 47 and 49-76 under 35 USC 103 are relevant to the

instant rejection. The arguments have been considered but have not been found persuasive for the reasons set forth above.

18 All other objections and rejections recited in Paper No. 36 are withdrawn.

19. No claims allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
March 20, 2000